

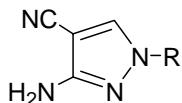
Supporting Information

Novel Highly Potent Adenosine Deaminase Inhibitors Containing the Pyrazolo[3,4-*d*]pyrimidine Ring System. Synthesis, Structure-Activity Relationships and Molecular Modeling Studies

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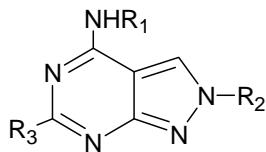
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Table 1. Spectral Data of 3-Amino-4-pyrazolecarbonitrile Derivatives **2 a-g,j-m**.



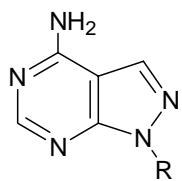
no.	R	IR (ν , cm ⁻¹)	¹ H-NMR (δ , ppm)
2a	(CH ₂) ₅ CH ₃	3329, 3218, 2213, 1658, 1571, 1527	0.84 (t, 3H, CH ₃), 1.22 (bs, 6H, CH ₂), 1.67 (t, 2H, NCH ₂ CH ₂), 3.84 (t, 2H, NCH ₂), 5.51 (s, 2H, NH ₂ , exc), 8.07 (s, 1H, H ₅)
2b	(CH ₂) ₆ CH ₃	3396, 3223, 2203, 1653, 1562, 1540	0.84 (t, 3H, CH ₃), 1.22 (bs, 8H, CH ₂), 1.61 (t, 2H, NCH ₂ CH ₂), 3.84 (t, 2H, NCH ₂), 5.52 (s, 2H, NH ₂ , exc), 8.06 (s, 1H, H ₅)
2c	(CH ₂) ₇ CH ₃	3394, 3208, 2216, 1664, 1560, 1520	0.84 (t, 3H, CH ₃), 1.22 (bs, 10H, CH ₂), 1.67 (t, 2H, NCH ₂ CH ₂), 3.83 (t, 2H, NCH ₂), 5.53 (s, 2H, NH ₂ , exc), 8.07 (s, 1H, H ₅)
2d	(CH ₂) ₈ CH ₃	3390, 3217, 2203, 1659, 1566, 1515	0.84 (t, 3H, CH ₃), 1.22 (bs, 12H, CH ₂), 1.65 (t, 2H, NCH ₂ CH ₂), 3.83 (t, 2H, NCH ₂), 5.50 (s, 2H, NH ₂ , exc), 8.06 (s, 1H, H ₅)
2f	(CH ₂) ₁₀ CH ₃	3384, 3214, 2216, 1651, 1600, 1518	0.84 (t, 3H, CH ₃), 1.22 (bs, 16H, CH ₂), 1.65 (t, 2H, NCH ₂ CH ₂), 3.83 (t, 2H, NCH ₂), 5.51 (s, 2H, NH ₂ , exc), 8.06 (s, 1H, H ₅)
2g	(CH ₂) ₁₁ CH ₃	3387, 3221, 2216, 1651, 1600, 1511	0.85 (t, 3H, CH ₃), 1.22 (bs, 18H, CH ₂), 1.67 (t, 2H, NCH ₂ CH ₂), 3.83 (t, 2H, NCH ₂), 5.52 (s, 2H, NH ₂ , exc), 8.06 (s, 1H, H ₅)
2j	CH ₂ CHOH(CH ₂) ₅ CH ₃	3385, 3414, 3234, 2229, 1631, 1593, 1533	0.85 (t, 3H, CH ₃), 1.23 (bs, 10H, CH ₂), 3.67-3.79 (m, 3H, NCH ₂ CH), 4.86 (d, 1H, OH, exc), 5.52 (s, 2H, NH ₂ , exc), 7.99 (s, 1H, H ₅)
2k	CH ₂ CHOH(CH ₂) ₇ CH ₃	3414, 3340, 3237, 2237, 1634, 1563, 1508	0.85 (t, 3H, CH ₃), 1.23 (bs, 14H, CH ₂), 3.65-3.85 (m, 3H, NCH ₂ CH), 4.85 (d, 1H, OH, exc), 5.52 (s, 2H, NH ₂ , exc), 7.99 (s, 1H, H ₅)
(R)-2k	CH ₂ CHOH(CH ₂) ₇ CH ₃	3416, 3339, 3231, 2233, 1634, 1557, 1520	0.84 (t, 3H, CH ₃), 1.23 (bs, 10H, CH ₂), 3.67-3.83 (m, 3H, NCH ₂ CH), 4.86 (d, 1H, OH, exc), 5.53 (s, 2H, NH ₂ , exc), 7.99 (s, 1H, H ₅)
(S)-2k	CH ₂ CHOH(CH ₂) ₇ CH ₃	3416, 3339, 3231, 2233, 1634, 1557, 1520	0.85 (t, 3H, CH ₃), 1.23 (bs, 10H, CH ₂), 3.72-3.79 (m, 3H, NCH ₂ CH), 4.85 (d, 1H, OH, exc), 5.53 (s, 2H, NH ₂ , exc), 7.99 (s, 1H, H ₅)
2l	CH(COCH ₃)(CH ₂) ₅ CH ₃	3414, 3332, 2210, 1717, 1649, 1567	0.80 (t, 3H, CH ₃ -9), 1.20 (bs, 8H, CH ₂ -5, CH ₂ -6, CH ₂ -7, CH ₂ -8), 1.86-1.93 (m, 2H, CH ₂ -4), 1.96 (s, 3H, CH ₃ -1), 4.75 (t, 1H, CH-3), 5.69 (s, 2H, NH ₂ , exc), 8.25 (s, 1H, H ₅)
2m	CH(CHOHCH ₃)(CH ₂) ₅ CH ₃	3443, 3330, 3221, 2220, 1726, 1625, 1557	0.83 (t, 3H, CH ₃ -9), 0.99 (d, 3H, CH ₃ -1), 1.21 (bs, 8H, CH ₂ -5, CH ₂ -6, CH ₂ -7, CH ₂ -8), 1.62-1.75 (m, 2H, CH ₂ -4), 3.65-3.75 (m, 2H, CH-2, CH-3), 4.75 (d, 1H, OH, exc), 5.50 (bs, 2H, NH ₂ , exc), 8.01 (s, 1H, H ₅)

Table 2. Spectral Data of Pyrazolo[3,4-*d*]pyrimidine Derivatives **3 a-l, 4** and **13**.



no.	R ₁	R ₂	R ₃	IR (ν , cm ⁻¹)	¹ H-NMR (δ , ppm)
3a	H	(CH ₂) ₅ CH ₃	H	3323, 3136, 1671, 1610, 1539	0.83 (t, 3H, CH ₃), 1.25 (bs, 6H, CH ₂), 1.84 (t, 2H, NCH ₂ CH ₂), 4.31 (t, 2H, NCH ₂), 7.55 (bs, 2H, NH ₂ , exc), 8.11 (s, 1H, H ₃), 8.27 (s, 1H, H ₆)
3b	H	(CH ₂) ₆ CH ₃	H	3309, 3126, 1668, 1602, 1531	0.83 (t, 3H, CH ₃), 1.23 (bs, 8H, CH ₂), 1.84 (t, 2H, NCH ₂ CH ₂), 4.30 (t, 2H, NCH ₂), 7.55 (bs, 2H, NH ₂ , exc), 8.11 (s, 1H, H ₃), 8.27 (s, 1H, H ₆)
3c	H	(CH ₂) ₇ CH ₃	H	3314, 3126, 1660, 1600, 1534	0.83 (t, 3H, CH ₃), 1.22 (bs, 10H, CH ₂), 1.84 (t, 2H, NCH ₂ CH ₂), 4.30 (t, 2H, NCH ₂), 7.55 (bs, 2H, NH ₂ , exc), 8.11 (s, 1H, H ₃), 8.27 (s, 1H, H ₆)
3d	H	(CH ₂) ₈ CH ₃	H	3323, 3130, 1668, 1611, 1527	0.83 (t, 3H, CH ₃), 1.22 (bs, 12H, CH ₂), 1.83 (t, 2H, NCH ₂ CH ₂), 4.30 (t, 2H, NCH ₂), 7.55 (bs, 2H, NH ₂ , exc), 8.11 (s, 1H, H ₃), 8.26 (s, 1H, H ₆)
3e	H	(CH ₂) ₉ CH ₃	H	3321, 3134, 1664, 1595, 1538	0.83 (t, 3H, CH ₃), 1.21 (bs, 14H, CH ₂), 1.83 (t, 2H, NCH ₂ CH ₂), 4.30 (t, 2H, NCH ₂), 7.57 (bs, 2H, NH ₂ , exc), 8.11 (s, 1H, H ₃), 8.27 (s, 1H, H ₆)
3f	H	(CH ₂) ₁₀ CH ₃	H	3323, 3123, 1664, 1590, 1539	0.85 (t, 3H, CH ₃), 1.23 (bs, 16H, CH ₂), 1.82 (t, 2H, NCH ₂ CH ₂), 4.32 (t, 2H, NCH ₂), 7.56 (bs, 2H, NH ₂ , exc), 8.12 (s, 1H, H ₃), 8.29 (s, 1H, H ₆)
3g	H	(CH ₂) ₁₁ CH ₃	H	3314, 3128, 1664, 1580, 1537	0.84 (t, 3H, CH ₃), 1.21 (bs, 18H, CH ₂), 1.84 (t, 2H, NCH ₂ CH ₂), 4.31 (t, 2H, NCH ₂), 7.82 (bs, 2H, NH ₂ , exc), 8.15 (s, 1H, H ₃), 8.32 (s, 1H, H ₆)
3h	H	CH ₂ C ₆ H ₅	H	3325, 3125, 1649, 1608, 1536	5.56 (s, 2H, CH ₂), 7.30-7.37 (m, 5H, ArH), 7.60 (bs, 2H, NH ₂ , exc), 8.11 (s, 1H, H ₃), 8.34 (s, 1H, H ₆)
3i	H	CH ₂ CH ₂ C ₆ H ₅	H	3320, 3135, 1653, 1600, 1535	3.20 (t, 2H, CH ₂), 4.61 (t, 2H, CH ₂), 7.14- 7.27 (m, 5H, ArH), 8.05 (bs, 2H, NH ₂ , exc), 8.21 (s, 1H, H ₃), 8.26 (s, 1H, H ₆)
3j	H	CH ₂ CHOH(CH ₂) ₅ CH ₃	H	3370, 3316, 3147, 1668, 1625, 1541	0.85 (t, 3H, CH ₃), 1.24 (bs, 10H, CH ₂), 4.08- 4.34 (m, 3H, NCH ₂ CH), 4.98 (d, 1H, OH, exc), 5.56 (bs, 2H, NH ₂ , exc), 8.11 (s, 1H, H ₃), 8.27 (s, 1H, H ₆)

3k	H	CH ₂ CHOH(CH ₂) ₇ CH ₃	H	3375, 3324, 3170, 1685, 1613, 1536	0.83 (t, 3H, CH ₃), 1.24 (bs, 12H, CH ₂), 1.34 (bs, 2H, CHCH ₂), 3.84 (bs, 1H, CH), 4.05- 4.35 (m, 2H, NCH ₂), 4.98 (dd, 1H, OH, exc), 7.57 (bs, 2H, NH ₂ , exc), 8.10 (s, 1H, H ₃), 8.27 (s, 1H, H ₆)
(R)-3k	H	CH ₂ CHOH(CH ₂) ₇ CH ₃	H	3375, 3324, 3170, 1685, 1613, 1536	0.84 (t, 3H, CH ₃), 1.24 (bs, 12H, CH ₂), 1.34 (bs, 2H, CHCH ₂), 3.84 (bs, 1H, CH), 4.08- 4.33 (m, 2H, NCH ₂), 4.99 (d, 1H, OH, exc), 7.57 (bs, 2H, NH ₂ , exc), 8.10 (s, 1H, H ₃), 8.27 (s, 1H, H ₆)
(S)-3k	H	CH ₂ CHOH(CH ₂) ₇ CH ₃	H	3375, 3324, 3170, 1685, 1613, 1536	0.83 (t, 3H, CH ₃), 1.20 (bs, 14H, CH ₂), 3.94 (bs, 1H, CH), 4.12-4.25 (m, 2H, NCH ₂), 4.81 (d, 1H, OH, exc), 7.69 (bs, 2H, NH ₂ , exc), 8.06 (s, 1H, H ₃), 8.13 (s, 1H, H ₆)
3l	H	CH(CHOHCH ₃)(CH ₂) ₅ CH ₃	H	3322, 3124, 1650, 1615, 1552	0.80 (t, 3H, CH ₃ -9), 1.00 (d, 3H, CH ₃ -1), 1.16 (bs, 8H, CH ₂ -5, CH ₂ -6, CH ₂ -7, CH ₂ -8), 1.76-1.96 (m, 2H, CH ₂ -4), 3.92-4.00 (m, 1H, CH-3), 4.12-4.22 (m, 1H, CH-2), 4.96 (d, 1H, OH, exc), 7.50 (bs, 2H, NH ₂ , exc), 8.10 (s, 1H, H ₃), 8.30 (s, 1H, H ₆)
4	COCH ₃	(CH ₂) ₉ CH ₃	H	3313, 3245, 3163, 1721, 1687, 1654, 1610	0.83 (t, 3H, CH ₃), 1.20 (bs, 14H, CH ₂), 1.58 (t, 2H, NCH ₂ CH ₂), 2.22 (s, 3H, COCH ₃), 4.43 (t, 2H, NCH ₂), 8.65 (s, 1H, H ₃), 8.73 (s, 1H, H ₆), 11.05 (s, 1H, NH, exc)
13	H	(CH ₂) ₉ CH ₃	C ₆ H ₅	3419, 3317, 3216, 1615, 1600, 1538	0.83 (t, 3H, CH ₃), 1.22 (bs, 14H, CH ₂), 1.57 (t, 2H, NCH ₂ CH ₂), 4.33 (t, 2H, NCH ₂), 7.43 (t, 3H, ArH), 7.64 (bs, 2H, NH ₂ , exc), 8.29 (s, 1H, H ₃), 8.37 (d, 2H, ArH)

Table 3. Spectral Data of 4-Amino-1-alkylpyrazolo[3,4-*d*]pyrimidine Derivatives **12 a-i**.

no.	R	IR (ν , cm ⁻¹)	¹ H-NMR (δ , ppm)
12a	(CH ₂) ₉ CH ₃	3367, 3144, 1657, 1591, 1557	0.83 (t, 3H, CH ₃), 1.19 (bs, 14H, CH ₂), 1.78 (t, 2H, NCH ₂ CH ₂), 4.24 (t, 2H, NCH ₂), 7.65 (bs, 2H, NH ₂ , exc), 8.05 (s, 1H, H ₃), 8.14 (s, 1H, H ₆)
12b	(CH ₂) ₁₀ CH ₃	3314, 3154, 1657, 1598, 1558	0.83 (t, 3H, CH ₃), 1.19 (bs, 16H, CH ₂), 1.77 (t, 2H, NCH ₂ CH ₂), 4.24 (t, 2H, NCH ₂), 7.65 (bs, 2H, NH ₂ , exc), 8.05 (s, 1H, H ₃), 8.14 (s, 1H, H ₆)
12c	(CH ₂) ₁₁ CH ₃	3330, 3126, 1654, 1590, 1562	0.83 (t, 3H, CH ₃), 1.20 (bs, 18H, CH ₂), 1.77 (t, 2H, NCH ₂ CH ₂), 4.24 (t, 2H, NCH ₂), 7.64 (bs, 2H, NH ₂ , exc), 8.05 (s, 1H, H ₃), 8.14 (s, 1H, H ₆)
12e	CH ₂ CH ₂ C ₆ H ₅	3370, 3324, 3119, 1654, 1598, 1562	3.13 (t, 2H, CH ₂), 4.49 (t, 2H, NCH ₂), 7.08-7.21 (m, 5H, ArH), 7.68 (bs, 2H, NH ₂ , exc), 8.05 (s, 1H, H ₃), 8.12 (s, 1H, H ₆)
12f	CH ₂ CHOH(CH ₂) ₅ CH ₃	3307, 3134, 1677, 1617, 1571	0.83 (t, 3H, CH ₃), 1.20 (bs, 10H, CH ₂), 4.08-4.34 (m, 3H, NCH ₂ CH), 4.98 (d, 1H, OH, exc), 5.56 (bs, 2H, NH ₂ , exc), 8.15 (s, 1H, H ₃), 8.20 (s, 1H, H ₆)
12g	CH(COCH ₃)(CH ₂) ₅ CH ₃	3375, 3332, 3172, 1712, 1658, 1562	0.77 (t, 3H, CH ₃ -9), 1.13 (bs, 8H, CH ₂ -5, CH ₂ -6, CH ₂ -7, CH ₂ -8), 1.85 (s, 3H, CH ₃ -1), 2.04-2.14 (m, 2H, CH ₂ -4), 5.36 (t, 1H, CH-3), 7.77 (bs, 2H, NH ₂ , exc), 8.07 (s, 1H, H ₃), 8.19 (s, 1H, H ₆)
12h	CH(CHOHCH ₃)(CH ₂) ₅ CH ₃	3412, 3331, 3180, 1661, 1556	0.76 (t, 3H, CH ₃ -9), 1.06-1.23 (m, 11H, CH ₂ -5, CH ₂ -6, CH ₂ -7, CH ₂ -8, CH ₃ -1), 1.65-1.75 (m, 2H, CH ₂ -4), 3.90-4.07 (m, 2H, CH-2, CH-3), 4.64 (d, 1H, OH, exc), 7.62 (bs, 2H, NH ₂ , exc), 8.07 (s, 1H, H ₃), 8.14 (s, 1H, H ₆)

ANALYTICAL DATA

no.	formula	Calcd. %			Found %		
		C	H	N	C	H	N
2a	C ₁₀ H ₁₆ N ₄	62.47	8.39	29.14	62.56	8.38	29.19
2b	C ₁₁ H ₁₈ N ₄	64.05	8.79	27.16	64.27	8.86	27.44
2c	C ₁₂ H ₂₀ N ₄	65.42	9.15	25.43	65.60	9.26	25.62
2d	C ₁₃ H ₂₂ N ₄	66.36	9.46	23.91	66.49	4.24	23.84
2f	C ₁₅ H ₂₆ N ₄	68.66	9.99	21.35	68.42	9.81	21.36
2g	C ₁₆ H ₂₈ N ₄	69.52	10.21	20.27	69.53	10.47	20.10
2j	C ₁₂ H ₂₀ N ₄ O	60.99	8.53	23.71	60.79	8.50	23.55
2k	C ₁₄ H ₂₄ N ₄ O	63.61	9.15	21.19	63.41	9.00	21.21
(R)-2k	C ₁₄ H ₂₄ N ₄ O	63.61	9.15	21.19	63.55	9.09	21.37
(S)-2k	C ₁₄ H ₂₄ N ₄ O	63.61	9.15	21.19	63.35	9.05	21.25
2l	C ₁₃ H ₂₀ N ₄ O	62.88	8.12	22.56	62.79	8.22	22.40
2m	C ₁₃ H ₂₂ N ₄ O	62.37	8.86	22.38	62.20	8.92	22.37
3a	C ₁₁ H ₁₇ N ₅	60.25	7.81	31.93	60.27	7.80	31.88
3b	C ₁₂ H ₁₉ N ₅	61.78	8.21	30.01	61.65	8.10	30.23
3c	C ₁₃ H ₂₁ N ₅	63.13	8.56	28.31	63.32	8.56	28.17
3d	C ₁₄ H ₂₃ N ₅	64.34	8.87	26.79	64.44	8.70	26.82
3e	C ₁₅ H ₂₅ N ₅	65.42	9.15	25.43	65.20	9.32	25.35
3f	C ₁₆ H ₂₇ N ₅	66.40	9.40	24.19	66.55	9.61	24.39
3g	C ₁₇ H ₂₉ N ₅	67.29	9.63	23.08	67.11	9.69	23.09
3h	C ₁₂ H ₁₁ N ₅	63.99	4.92	31.09	63.90	4.90	31.00
3i	C ₁₃ H ₁₃ N ₅	65.26	5.48	29.27	65.23	5.44	29.24
3j	C ₁₃ H ₂₁ N ₅ O	59.29	8.04	26.59	59.25	8.02	26.55
3k	C ₁₅ H ₂₅ N ₅ O	61.83	8.65	24.03	61.78	8.66	24.00
(R)-3k	C ₁₅ H ₂₅ N ₅ O	61.83	8.65	24.03	61.80	8.55	23.99
(S)-3k	C ₁₅ H ₂₅ N ₅ O	61.83	8.65	24.03	61.66	8.65	24.09
3l	C ₁₄ H ₂₃ N ₅ O	60.62	8.36	25.25	60.63	8.33	25.22
4	C ₁₇ H ₂₇ N ₅ O	64.32	8.57	22.06	64.31	8.55	22.01
6	C ₁₆ H ₃₆ O ₂ Si	66.60	12.58	...	66.45	12.33	...
7	C ₁₇ H ₃₈ O ₄ SSi	55.69	10.45	...	55.59	10.32	...

8	C ₁₁ H ₂₄ O ₄ S	52.35	9.59	...	52.47	9.44	...
9	C ₁₀ H ₂₀ O	76.86	12.90	...	76.56	12.77	...
12a	C ₁₅ H ₂₅ N ₅	65.42	9.15	25.43	65.37	9.14	25.40
12b	C ₁₆ H ₂₇ N ₅	66.40	9.40	24.20	66.39	9.36	24.25
12c	C ₁₇ H ₂₉ N ₅	67.29	9.63	23.08	67.27	9.60	23.00
12e	C ₁₃ H ₁₅ N ₅	64.71	6.27	29.02	64.67	6.11	29.00
12f	C ₁₃ H ₂₁ N ₅ O	59.29	8.04	26.59	59.28	8.00	26.55
12g	C ₁₄ H ₂₁ N ₅ O	61.07	7.69	25.43	61.07	6.63	25.41
12h	C ₁₄ H ₂₃ N ₅ O	60.62	8.36	25.25	60.63	8.33	25.29
12i	C ₇ H ₉ N ₅ O	46.92	5.06	39.08	46.90	5.08	39.01
13	C ₁₅ H ₁₆ N ₄ O	67.15	6.01	20.88	67.00	6.02	20.68